

EXHIBIT A

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 1 of 18

Claims

1. A homogeneous crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14, and 26.91.
2. The polymorph of claim 1, characterized by the X-ray powder diffraction pattern shown in Figure 3.
3. A crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, which is free of the A polymorph.
4. The polymorph of claim 3, characterized by the X-ray powder diffraction pattern shown in Figure 3.
5. A composition comprising a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, and a carrier, wherein the composition is free of the A polymorph.

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 2 of 18

6. The composition of claim 5, wherein the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately:

2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)
6.255	100.0	17.668	2.5	22.982	4.8	27.534	0.9	32.652	1.7
7.860	3.2	18.193	0.7	23.589	2.3	28.148	0.5	33.245	1.7
9.553	3.9	18.749	1.5	23.906	3.0	28.617	0.3	34.719	1.5
11.414	1.5	19.379	1.0	24.459	6.8	29.000	0.4	35.737	0.8
12.483	6.4	20.196	14.4	25.138	10.0	29.797	0.1	36.288	1.0
13.385	9.6	20.734	4.2	25.617	3.7	30.267	0.9	36.809	0.6
14.781	2.1	21.103	14.4	25.908	3.9	30.900	1.6	37.269	1.1
15.720	2.9	21.873	4.7	26.527	2.8	31.475	0.2	37.643	1.4
16.959	5.5	22.452	4.5	26.911	5.6	31.815	0.4	38.114	1.7

7. The composition of claim 5, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the polymorph B form is characterized by the X-ray powder diffraction pattern shown in Figure 3.

8-13. (canceled)

14. A method of treating abnormal cell growth of a cell expressing the epidermal growth factor receptor (EGFR) in a mammal which comprises administering to said mammal a therapeutically effective amount of the polymorph of claim 3, wherein the abnormal cell growth is brain cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, glioblastoma multiforme breast cancer, head cancer, neck cancer, esophageal cancer, prostate cancer, colorectal cancer, lung cancer, renal cancer, kidney cancer, ovarian cancer, gynecological cancer, thyroid cancer, nor-small cell lung

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 3 of 18

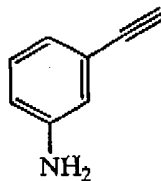
cancer (NSCLC), refractory ovarian cancer, or head and neck cancer.

15. The method of claim 14, wherein the abnormal cell growth is brain, squamous cell, bladder, gastric, pancreatic, hepatic, glioblastoma multiforme breast, head, neck, esophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological or thyroid cancer.
16. The method of claim 14, wherein the abnormal cell growth is non-small cell lung cancer (NSCLC), refractory ovarian cancer, or head and neck cancer.
17. The method of claim 14, wherein the therapeutically effective amount is from about 0.001 to about 100 mg/kg/day.
18. The method of claim 14, wherein the therapeutically effective amount is from about 1 to about 35 mg/kg/day.
19. The method of claim 14, wherein the therapeutically effective amount is from about 1 to about 7000 mg/day.
20. The method of claim 19, wherein the therapeutically effective amount is from about 5 to about 2500 mg/day.
21. The method of claim 20, wherein the therapeutically effective amount is from about 5 to about 200 mg/day.
22. The method of claim 21, wherein the therapeutically effective amount is from about 25 to about 200 mg/day.
23. A method for the treatment of abnormal cell growth of a cell expressing the epidermal growth factor receptor (EGFR) in a mammal which comprises administering to said mammal a therapeutically effective amount of the

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 4 of 18

polymorph of claim 3 in combination with an anti-tumor agent selected from the group consisting of a mitotic inhibitor, an alkylating agent, an anti-metabolite, an intercalating antibiotic, a growth factor inhibitor, a cell cycle inhibitor, an enzyme, a topoisomerase inhibitor, a biological response modifier, an anti-hormone, and an anti-androgen.

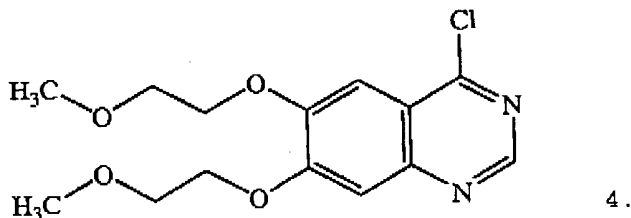
24. A process for preparing a crystalline polymorph of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride designated the B polymorph, which is free of the A polymorph, which comprises the step of recrystallizing N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in a solvent comprising alcohol.
25. The process of claim 24, wherein the solvent further comprises water.
26. The process of claim 24, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride is prepared by coupling a compound of formula 6



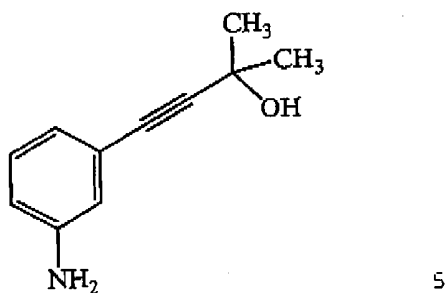
6

with a compound of formula 4

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 5 of 18

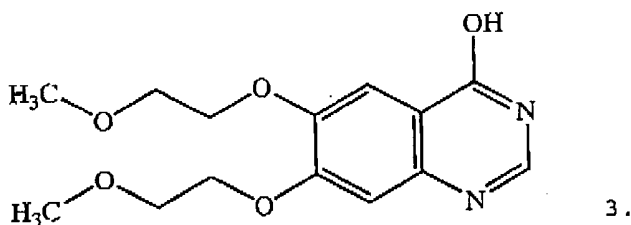


27. The process of claim 26, wherein said compound of formula 6 is prepared by heating a compound of formula 5



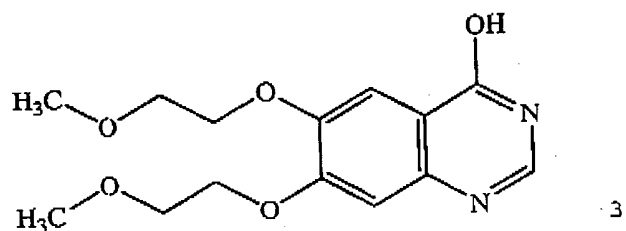
in a suspension of metal alkali and solvent.

28. The process of claim 26, wherein said compound of formula 4 is prepared by chlorinating a compound of formula 3

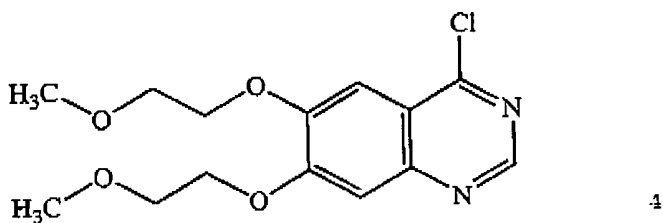


29. A process for the production of the polymorph B of claim 1 comprising the steps of:
- a) substitution chlorination of a compound of formula 3

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 6 of 18

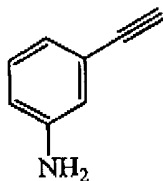


having an hydroxyl group, to provide a compound of formula 4



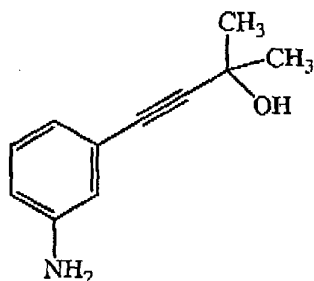
by reaction thereof in a solvent mixture of thionyl chloride, methylene chloride and dimethylformamide;

b) preparation of a compound of formula 6



in situ from starting material of compound of formula 5

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 7 of 18



5

by heating the compound of formula 5 in a suspension of metal alkali and solvent;

- c) reaction of the compound of formula 6 in situ with the compound of formula 4 wherein the compound of formula 6 replaces the chlorine in the compound of formula 4 to give the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride; and
- d) recrystallizing the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, in alcohol, into the polymorph B form.
30. The process of claim 29, wherein the substitution chlorination is quenched in the presence of aqueous sodium hydroxide.
31. The process of claim 29, wherein the substitution chlorination is quenched in the presence of aqueous sodium bicarbonate.
32. The process of claim 29, wherein the substitution chlorination is quenched in the presence of aqueous potassium hydroxide, aqueous potassium bicarbonate, aqueous potassium carbonate, aqueous sodium carbonate, or a mixture thereof.
- 33-49. (canceled)

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 8 of 18

50. A method of inhibiting the development of basal or squamous cell carcinoma of the skin in areas exposed to the sun or in persons of high risk to said carcinoma, said method comprising administering to said persons a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, or pharmaceutically acceptable salts thereof in anhydrous or hydrate forms, and a carrier, so as to thereby inhibit the development of basal or squamous cell carcinoma of the skin.
51. (canceled)
52. A process of making a composition which composition comprises a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, which is free of the A polymorph, comprising admixing the crystalline polymorph with a carrier.
53. The process of claim 52, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the polymorph B form is characterized by the X-ray powder diffraction pattern shown in Figure 3.
54. The process of claim 52, wherein the carrier is a pharmaceutically acceptable carrier.
- 55-57. (canceled)

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 9 of 18

58. A pharmaceutical composition which comprises a therapeutically effective amount of the polymorph of claim 3 and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is free of the A polymorph.
59. The pharmaceutical composition of claim 58, wherein said composition is adapted for oral administration.
60. The pharmaceutical composition of claim 59, wherein the pharmaceutical composition is in the form of a tablet.
61. A process for the production of a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph by recrystallization comprising the steps of:
- heating to reflux alcohol, water and the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine so as to form a solution;
 - cooling the solution to between about 65 and 70° C;
 - clarifying the solution; and
 - precipitating polymorph B by further cooling the clarified solution.

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 10 of 18

62. A composition consisting of a homogeneous crystalline polymorph of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the form of polymorph B, which is characterized by the following peaks:

Polymorph B

Anode: Cu - Wavelength 1 1.54056 Wavelength 2: 1.54439 (Rel Intensity:0.500)
Range # 1 - Coupled 3.000 to 40.040 StepSize: 0.040 StepTime 1.00
Smoothing Width: 0.300 Threshold: 1.0

d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)
14.11826	100.0	5.01567	2.5	3.86656	4.8	3.23688	0.9	2.74020	1.7
11.23947	3.2	4.87215	0.7	3.76849	2.3	3.16755	1.5	2.69265	1.7
9.25019	3.9	4.72882	1.5	3.71927	3.0	3.11673	4.3	2.58169	1.5
7.74623	1.5	4.57666	1.0	3.63632	6.8	3.07644	1.4	2.51043	0.8
7.08519	6.4	4.39330	14.4	3.53967	10.0	2.99596	2.1	2.47356	1.0
6.60941	9.6	4.28038	4.2	3.47448	3.7	2.95049	0.9	2.43974	0.6
5.98828	2.1	4.20645	14.4	3.43610	3.9	2.89151	1.6	2.41068	1.1
5.63253	2.9	4.06007	4.7	3.35732	2.8	2.83992	2.2	2.38755	1.4
5.22369	5.5	3.95667	4.5	3.31029	5.6	2.81037	2.4	2.35914	1.7

or,

Polymorph B

Anode: Cu - Wavelength 1 1.54056 Wavelength 2: 1.54439 (Rel Intensity:0.500)
Range# 1 - Coupled: 3.000 to 40.040 StepSize 0.040 StepTime: 1.00
Smoothing Width:0.300 Threshold: 1.0

2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)
6.255	100.0	17.668	2.5	22.982	4.8	27.534	0.9	32.652	1.7
7.860	3.2	18.193	0.7	23.589	2.3	28.148	1.5	33.245	1.7
9.553	3.9	18.749	1.5	23.906	3.0	28.617	4.3	34.719	1.5
11.414	1.5	19.379	1.0	24.459	6.8	29.000	1.4	35.737	0.8
12.483	6.4	20.196	14.4	25.138	10.0	29.797	2.1	36.288	1.0
13.385	9.6	20.734	4.2	25.617	3.7	30.267	0.9	36.809	0.6
14.781	2.1	21.103	14.4	25.908	3.9	30.900	1.6	37.269	1.1
15.720	2.9	21.873	4.7	26.527	2.8	31.475	2.2	37.643	1.4
16.959	5.5	22.452	4.5	26.911	5.6	31.815	2.4	38.114	1.7

and at least one carrier.

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 11 of 18

63. A method of treating a subject with a tumor by inducing differentiation of tumor cells expressing an epidermal growth factor receptor (EGFR) in the tumor comprising contacting the cells with an effective amount of the compound of claim 3, or a composition of claim 5 so as to thereby treat the subject, wherein the tumor is brain cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, glioblastoma multiforme breast cancer, head cancer, neck cancer, esophageal cancer, prostate cancer, colorectal cancer, lung cancer, renal cancer, kidney cancer, ovarian cancer, gynecological cancer, thyroid cancer, non-small cell lung cancer (NSCLC), refractory ovarian cancer, or head and neck cancer.
64. A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), Barrett's esophagus (pre-malignant syndrome), or neoplastic cutaneous diseases in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, or pharmaceutically acceptable salts thereof in anhydrous or hydrate forms, and a carrier.
65. The method of claim 64, wherein the treatment further comprises a palliative or neo-adjuvant/adjuvant monotherapy.
66. The method of claim 64, wherein the treatment further comprises blocking epidermal growth factor receptors (EGFR).

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 12 of 18

67. The method of claim 64, for use in treatment of tumors that express EGFRvIII.
68. The method of claim 64, wherein the treatment further comprises a combination with any of chemotherapy and immunotherapy.
69. The method of claim 64, wherein the treatment further comprises, treatment with either or both anti-EGFR and anti-EGF antibodies.
70. The method of claim 64, wherein the treatment further comprises a further administration to said mammal of a member of the group consisting of inhibitors of MMP (matrix-metallo-proteinase), VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, CTLA₄ (cytotoxic T-lymphocyte antigen 4) and erbB2, MAb to VEGFr, rhuMAb-VEGF, erbB2 MAb and avb3 Mab
71. The method of claim 64, wherein the pharmaceutical composition is used as radiation sensitizers for cancer treatment or in combination with anti-hormonal therapies.
72. The method of claim 64, wherein the pharmaceutical composition is used for the inhibition of tumor growth in humans in a regimen with radiation treatment.
73. (canceled)
74. A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), endometrial cancer, glioma, melanoma, Barrett's esophagus (pre-malignant syndrome), adrenal and skin cancers or neoplastic cutaneous diseases in a mammal comprising administering to said mammal a therapeutically effective

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 13 of 18

amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, or pharmaceutically acceptable salts thereof in anhydrous or hydrate forms,

wherein the treatment further comprises,

a) treatment with either or both anti-EGFR and anti-EGF antibodies,

b) administration to said mammal of a member of the group consisting of inhibitors of MMP (matrix-metalloproteinase), VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, CTLA₄ (cytotoxic T-lymphocyte antigen 4) and erbB2, MAb to VEGFr, rhuMAb-VEGF, erbB2 MAb and avb3 Mab, or

c) radiation treatment.

75. The method of claim 15, wherein the abnormal cell growth is pancreatic cancer.
76. The method of claim 15, wherein the abnormal cell growth is colorectal cancer.
77. The method of claim 15, wherein the abnormal cell growth is prostate cancer.
78. The method of claim 15, wherein the abnormal cell growth is breast cancer.
79. The method of claim 15, wherein the abnormal cell growth is esophageal cancer.
80. The method of claim 15, wherein the abnormal cell growth is ovarian cancer.

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 14 of 18

81. The method of claim 15, wherein the abnormal cell growth is glioblastoma multiforme.
82. The method of claim 15, wherein the abnormal cell growth is hepatic cancer.
83. The method of claim 15, wherein the abnormal cell growth is renal cancer.
84. The method of claim 15, wherein the abnormal cell growth is gastric cancer.
85. The method of claim 15, wherein the abnormal cell growth is bladder cancer.
86. The method of claim 16, wherein the abnormal cell growth is non-small cell lung cancer (NSCLC).
87. The method of claim 16, wherein the abnormal cell growth is head and neck cancer.
88. The method of claim 64 for the treatment of non-small cell lung cancer (NSCLC).
- 89-91. (canceled)
92. A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), endometrial cancer, glioma, melanoma, Barrett's esophagus (pre-malignant syndrome), adrenal cancers or neoplastic cutaneous diseases in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 15 of 18

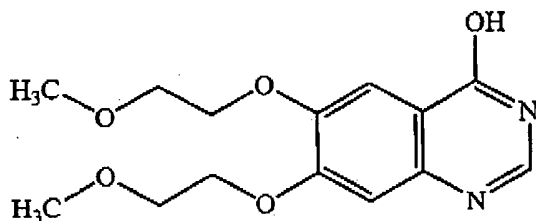
designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, which is free of the A polymorph, and a pharmaceutically acceptable carrier.

93. The method of claim 92, wherein the treatment further comprises a palliative or neo-adjuvant/adjuvant monotherapy.
94. The method of claim 92, wherein the treatment further comprises blocking epidermal growth factor receptors (EGFR).
95. The method of claim 92, for use in treatment of tumors that express EGFRvIII.
96. The method of claim 92, wherein the treatment further comprises a combination with any of chemotherapy and immunotherapy.
97. The method of claim 92, wherein the treatment further comprises, treatment with either or both anti-EGFR and anti-EGF antibodies.
98. The method of claim 92, wherein the treatment further comprises a further administration to said mammal of a member of the group consisting of inhibitors of MMP (matrix-metallo-proteinase), VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, CTLA₄ (cytotoxic T-lymphocyte antigen 4) and erbB2, MAb to VEGFr, rhuMAb-VEGF, erbB2 MAb and avb3 MAb.

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 16 of 18

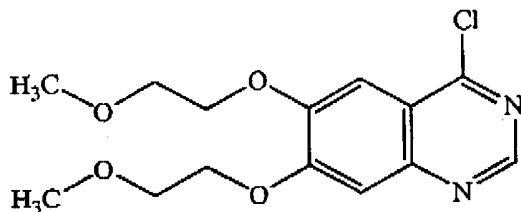
99. The method of claim 92, wherein the pharmaceutical compounds are used as radiation sensitizers for cancer treatment or in combination with anti-hormonal therapies.
100. The method of claim 92, wherein the pharmaceutical compounds are used for the inhibition of tumor growth in humans in a regimen with radiation treatment.
101. The method of claim 92 for the treatment of glioma.
102. The method of claim 92 for the treatment of melanoma.
103. The pharmaceutical composition of claim 53, wherein the therapeutically effective amount is from 1 to 7000 mg.
104. The pharmaceutical composition of claim 103, wherein the therapeutically effective amount is from 5 to 2500 mg.
105. The pharmaceutical composition of claim 104, wherein the therapeutically effective amount is from 100 to 1600 mg.
106. The pharmaceutical composition of claim 103, wherein the therapeutically effective amount is from 5 to 200 mg.
107. The pharmaceutical composition of claim 106, wherein the therapeutically effective amount is from 25 to 200 mg.
108. The method of claim 14, wherein the therapeutically effective amount is from 100 to 1600 mg/week.
109. The method of claim 14, wherein the therapeutically effective amount of the polymorph is administered weekly.
110. A process for the production of the polymorph B of claim 3 comprising the steps of:
 - a) substitution chlorination of a compound of formula 3

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 17 of 18



3

having an hydroxyl group, to provide a compound of formula 4

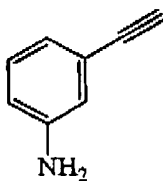


4

by reaction thereof in a solvent mixture of thionyl chloride, methylene chloride and dimethylformamide;

b) quenching the substitution chlorination in the presence of aqueous sodium bicarbonate;

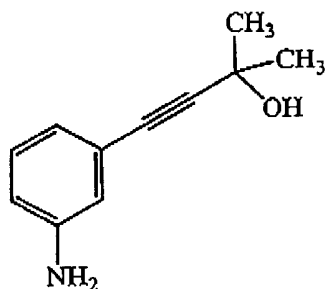
c) preparation of a compound of formula 6



6

in situ from starting material of compound of formula 5

Applicant: Timothy Norris et al.
Serial No.: 09/711,272
Filed: November 9, 2000
Page 18 of 18



by heating the compound of formula 5 in a suspension of metal alkali and solvent;

- d) reaction of the compound of formula 6 in situ with the compound of formula 4 wherein the compound of formula 6 replaces the chlorine in the compound of formula 4 to give the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride; and
- e) recrystallizing the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, in alcohol, into the polymorph B form.